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Upper Respiratory Infections[*]

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INTRODUCTION

The term "upper respiratory" infections is widely used and includes the disease influenza in which we are vitally interested and which will be discussed in this report. Influenza is primarily a clinical and epidemiological syndrome that appears in epidemic waves of different proportions. Occurring at a time when illness of epidemic type is wide-spread various forms of infectious disease have been loosely termed influenza (such as colds, grippe, glandular fever, intestinal influenza, and many other clinical manifestations with similar symptoms).

There is little agreement among clinicians as to the definition of "influenza." According to Francis's definition influenza is an acute infectious respiratory disease occurring in epidemics of varying extent and severity, characterized by rapid dissemination, high mortality, sudden onset with fever, myalgias, pharyngitis, cough, leukopenia, and inconstant bronchitis or pneumonitis. Recovery is generally prompt after three to four days, but a marked residual fatigue may persist.

Since the clinical picture of influenza is very similar to the initial symptoms in a number of acute upper respiratory illnesses, many attempts to establish definite criteria based upon epidemiological, clinical and laboratory standards have been attempted. Epidemiologically the terms pandemic, epidemic, and sporadic influenza have been used. Clinically the common cold, grippe, intestinal influenza are terms applied in an effort to differentiate from true influenza. White blood counts and the isolation of Pfeiffer's bacillus have been employed as laboratory diagnostic aids. However, none of the methods used have been of sufficient significance to lead to a definite diagnosis.

HISTORICAL REVIEW

In recent years knowledge pertaining to a group of infectious agents other than the characteristic bacteria has been greatly advanced. The group referred to is the minute ultra-microscopic agents called filterable viruses. In 1931 Shope published the first of his papers in which he established the fact that swine influenza was produced by a filterable virus in symbiosis with a hemophilic bacterium, H. influenzae suis. The virus agent was found to be the essential component in the cause and dissemination of the disease and in the immunity which followed infection. The bacterium appeared only to increase the severity of the disease induced by the virus.

In 1933 Smith, Andrewes and Laidlaw in England recovered a strain of virus by inoculating intranasally into ferrets the bacteria-free filtrates of nasal washings from acutely ill patients. The disease was transmissible from sick ferrets to normal animals by suspensions of nasal turbinates or by contact. Recovered animals were immune to reinfection, and their serum contained antibodies capable of neutralizing the virus. The same investigators reported that ferrets were also susceptible to the swine strain and that there was a relationship between the two. In 1934 Shope found that if ferrets were anesthetized at the time of their inoculation with swine influenza virus, an extensive pneumonia developed.

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[*] Read before the Health Officers' Section, League of California Municipalities, San Jose, Sept. 14, 1937.

In the same year Francis was successful in isolating a strain of virus in ferrets from human material sent from Puerto Rico; after a period of adaptation the human influenza virus also produced lung lesions in infected ferrets. Again, Francis and Magill at the Rockefeller Institute, and Andrewes, Laidlaw, and Smith in England, independently reported the susceptibility of white mice to human strains. In mice, a fatal disease occurs with intensive non-bacterial pneumonia. The recognition of the susceptibility of mice was doubly advantageous inasmuch as it eliminated for many purposes the use of the ferret and was readily adaptable to studies of immunity. Since the etiology of epidemic influenza has been proved, our knowledge is making marked progress in the diagnosis of this disease and its relation to other upper respiratory infections. This report proposes to review some aspects of the recent experimental work on influenza.

RECENT ADVANCES

Size

The virus of influenza behaves as other agents belonging to the group of filterable viruses. The size of the virus has been measured by ultra-centrifugation and ultra-filtration. The technical methods will not be considered here. In 1936 by means of ultrafiltration methods with graded collodion membranes, Elford, Andrewes, and Tang have shown that both the human and swine viruses are of the probable size of 80 to 120 mille microns. This is smaller than the viruses of vaccinia and herpes, and considerably smaller than the ordinary bacteria. According to these investigators it appears extremely improbable that the viruses can represent a minute form of Haemophilus influenzae, or of any other bacterium which has been suggested as the cause of influenza.

Strains

Strains of virus have been obtained from both man and animal. As stated above the swine virus was recovered by Shope in 1930 from hogs in Iowa. Human strains have been isolated from material obtained in Puerto Rico, Alaska, Philadelphia, New York, Mississippi, and Missouri by Francis and his co-workers. Strains were also recovered from human sources in Chicago and New Haven. Andrewes, Laidlaw, and Smith during epidemics of influenza in England obtained several strains from similar sources. Investigators in Russia, Australia, and Budapest report viruses in patients suffering with influenza.

A comparison of the viruses from animal and human origin showed them to be immunologically distinct entities but still related. Whereas, those isolated from humans in various localities were immunologically identical. According to Francis, however, certain differences exist in the severity of the experimental disease in animals produced by various human strains. These differences are reflected to a certain extent in the severity of the disease which the respective strains incite in the human population. Variations also appear in the susceptibility of animals to the different strains.

SUSCEPTIBILITY OF ANIMALS

A number of animal species has been employed for experimental work in influenza. The ferret gives the most successful and consistent results. As stated above some strains, i.e., P.R. 8 produce an extensive pulmonary consolidation in the lungs. Other strains, such as Alaska, cause no lung involvement. The turbinates, however, are usually involved in either case. The incubation period in ferrets is from 24 to 48 hours—after which the animal develops a temperature which continues for a few days, then drops to normal, followed by a secondary rise. By the use of turbinates or lungs from infected animals, serial passage is very easily effected in ferrets with both swine and human strains.

In 1935, Shope infected mice directly, using swine virus without intervening ferret passage. Previously, it was thought necessary to pass human strains to a ferret before the virus could be adapted to white mice, but in 1937 Francis and Magill at the Rockefeller Institute, and Clampit and Gordan in Chicago, working independently were able to infect mice directly with material from patients acutely ill with influenza. Several passages were required before the strain could be established and visible pulmonary lesions observed. Guinea pigs and rabbits have been inoculated and found refractory to infection with influenza virus. In 1936, Stuart-Harris passed the infection to hedge hogs, producing a disease primarily of the nasal mucous membranes, and more recently a group of Russian investigators report the susceptibility of the rat to the virus of influenza.

VIABILITY OF THE VIRUS

This virus may be preserved for long periods of time without destroying it. Material for storing is obtained from the lungs of infected mice and ferrets, from the turbinates of infected ferrets, and from tissue cultures. The virus may be held for several months in 50 per cent glycerine and Locke's solution under a vaseline seal at ordinary ice box temperature, or, it may be put into a tube without liquid, sealed, and placed in a thermos containing alcohol and dry ice. The temperature of this mixture is minus 80° C. The virus remains viable for a number of months at this low temperature. A third method of preservation is freezing, drying, and sealing in a vacuum. This last procedure is probably the most effective for holding the virus and for shipping purposes.

Although the virus withstands extremely low temperatures the English workers report that it is killed by heating for one hour at 56° C. An interesting observation is the fact that the material may be diluted to a great extent and still cause death in mice. At the Rockefeller Institute the standard for killing mice is usually 10 to the minus 6 or 1 to 1,000,000 dilution, and lesions are produced at 10 to the minus 7 or 1 to 10,000,000. Russian workers report lesions after several passages in mice at a dilution of 10 to the minus 12.

CULTIVATION OF VIRUS

Animals were employed exclusively for the maintenance of strains in the experimental laboratories. In 1935, Burnet, however, reported the successful adaptation of the virus to growth on the chorioallantoic membrane of the developing egg. This observation has been confirmed by Francis and Magill at the Rockefeller Institute. Another advancement and one of greater potentialities is the use of tissue cultures. In 1935, the Rockefeller group succeeded in cultivating both human and swine strains of influenza virus in an artificial medium, which consists of Tyrode's solution with pieces of minced 12 day old chick embryo added. The flasks are incubated at 37° C. and transferred at 48 hour intervals. The cultures are checked for bacterial contamination at each transfer and mice are inoculated intranasally at intervals. After many transplants the virus is still virulent for mice and ferrets, and cultures are capable of inducing an active immunity in animals vaccinated subcutaneously or intraperitoneally. All cultures were initiated with tissues from infected mice of ferrets until the influenza epidemic of 1936-1937 when Francis and Magill obtained throat washings in Tyrode's solution. They contrifuged and filtered this material and planted it in tissue culture flasks. The virus was able to grow and multiply without intervening ferret or mouse passage.

The cultivation of virus in controlled tissue cultures has opened many possibilities for experimental study.

IMMUNITY

The question of immunity is one of prime interest and has caused a great deal of debate. Since it is particularly difficult to interpret the frequent reappearance year after year of influenza in previously infected individuals, the reports of investigators about the solid immunity of ferrets to reinfection are interesting and encouraging. After an indefinite period of five months or more, there occurs some decrease in the immunity as measured by mouse protection tests neutralizing a known virus. To date, it has not been found possible to infect mice by any route other than the respiratory tract. When the virus is inoculated subcutaneously or intraperitoneally even in large amounts, no signs of illness are observed at the first passage. Ferrets so treated develop circulating antibodies but do not become completely resistant to intranasal infection. Vaccination with living human influenza virus induces in the ferret a state of immunity somewhat similar to that exhibited by recovered animals after a lapse of months In mice, on the other hand, repeated subcutaneous or intraperitoneal injections of virus produce not only antibodies but also a solid immunity to intranasal injections with many lethal doses of the infectious agent. Francis believes that possibly this immunity is as complete as that which occurs in recovered mice.

The problem of immunity to influenza in human individuals is beset with many difficulties, the most important of which is probably diagnosis. Influenza is often merely a convenient label for some upper respiratory infection of unknown etiology. The epidemiological evidence of outbreaks is contradictory in many ways since all such epidemics are usually considered the same disease.

(Continued in next issue)

MOST CALIFORNIA BABIES BORN IN HOSPITALS

There were 84,460 live births in California in 1936. Of these, 63,366 occurred in licensed maternity homes and hospitals. This represents almost 75 per cent of the total. Of these 63,366 institutional births, 50,000 occurred in 341 hospitals and maternity homes, and more than 13,000 occurred in county hospitals.

In 1935 there were 55,443 institutional births in California. Almost 70 per cent of the total number of all the births that occurred in the whole state. Institutional births in 1936 show an increase of almost 8,000 over the preceding year.

There were 201 maternal deaths in institutions in 1936 as compared with 209 such deaths in 1935.

There were 1444 infant deaths in these institutions in 1936 as compared with 1593 such deaths in 1935.

The following table summarizes data pertaining to institutional births, deaths and maternal deaths in licensed maternity homes and hospitals of California in 1936:

Summary, 1936, Maternity Home and Hospital Reports

No. reporting		Mothers confined	Caesarean operations	Other oper. del.	No. live births	No. maternal deaths	No. infant deaths	No. still births
52	Co. Hospitals---	13,672	314	1,427	13,373	80	414	475
431	Licensed Homes and Hospitals--	50,535	2,489	5,415	49,993	121	1,030	1,010
	TOTALS ----	64,207	2,803	6,842	63,366	201	1,444	1,485

MORBIDITY

Complete Reports for Following Diseases for Week Ending September 11, 1937

Chickenpox

44 cases: Berkeley 2, Oakland 3, Piedmont 10, Angels Camp 1, Humboldt County 1, Los Angeles County 3, Los Angeles 6, Monterey Park 1, San Diego 2, San Francisco 9, Santa Barbara County 3, Healdsburg 1, Ventura County 1, Oxnard 1.

Diphtheria

21 cases: Alameda County 1, Oakland 1, Los Angeles County 3, Los Angeles 6, Pasadena 1, Santa Monica 1, Napa County 1, San Diego County 2, San Diego 1, San Mateo County 2, Santa Clara County 1, San Jose 1.

German Measles

18 cases: Berkeley 1, Los Angeles 3, Pasadena 1, Monterey Park 1, Orange County 1, Anaheim 1, San Diego 2, San Joaquin County 7, Sonoma County 1.

Influenza

11 cases: Kern County 1, Kings County 1, Alhambra 1, Los Angeles 4, Bell City 1, San Francisco 2, Sonoma County 1.

Malaria

8 cases: Kings County 3, Tulare County 2, Marysville 1, California 2.*

Measles

23 cases: Oakland 1, Kern County 1, Inglewood 1, Long Beach 2, Los Angeles 7, Signal Hill 1, Monterey County 1, Fullerton 1, Sacramento 1, San Diego 3, San Joaquin County 2, Santa Cruz 2.

Mumps

54 cases: Berkeley 1, Oakland 5, Piedmont 1, Fresno 1, Los Angeles County 1, Los Angeles 7, San Gabriel 1, San Marino 1, Anaheim 1, Fullerton 4, Sacramento 4, Ontario 1, San Diego County 4, Chula Vista 1, San Diego 2, San Francisco 12, Daly City 2, Santa Clara County 3, Gilroy 1, Sonoma County 1.

Pneumonia

24 cases: Fresno County 1, Kern County 1, Los Angeles 9, Madera County 1, Merced 1, Sacramento 1, San Bernardino County 1, Ontario 1, San Francisco 4, Santa Barbara 1, Sonoma County 2, Tulare County 1.

Scarlet Fever

66 cases: Alameda County 2, Oakland 4, Contra Costa County 1, Fresno County 3, Fresno 1, Glenn County 1, Kern County 1, Kings County 3, Los Angeles County 7, Alhambra 1, Huntington Park 1, Long Beach 1, Los Angeles 14, San Rafael 1, Orange County 4, Ontario 1, Chula Vista 2, San Francisco 4, Manteca 1, Stockton 2, San Mateo County 1, Santa Barbara County 1, Palo Alto 1, San Jose 1, Sonoma County 1, Tulare County 1, Sonora 1, Oxnard 1, Yolo County 1, Marysville 2.

Smallpox

2 cases: San Diego 2.

Typhoid Fever

29 cases: Oakland 1, Fresno County 2, Humboldt County 1, Kings County 1, Los Angeles County 1, Santa Monica 1, Merced County 2, Merced 1, Napa 1, Colfax 1, Riverside County 2, San Bernardino County 2, San Francisco 2, San Joaquin County 1, Santa Clara County 2, Tulare County 3, California 5.*

Whooping Cough

202 cases: Berkeley 3, Oakland 15, Contra Costa County 9, Fresno County 5, Fresno 5, Kern County 1, Los Angeles County 21, Alhambra 4, Culver City 3, Long Beach 2, Los Angeles 34, Monrovia 1, Pasadena 5, San Fernando 2, Merced County 1, Salinas 2, Anaheim 1, Riverside County 1, Riverside 2, Sacramento 8, San Bernardino County 1, Ontario 1, San Diego County 4, San Diego 17, San Francisco 18, San Joaquin County 5, Stockton 5, San Mateo County 2, Santa Barbara County 1, San Jose 3, Santa Cruz County 1, Santa Cruz, 13, Solano County 1, Tulare County 3, Ventura County 2.

Meningitis (Epidemic)

2 cases: Imperial County 1, Stockton 1.

Dysentery (Amoebic)

3 cases: San Francisco 1, Sutter County 1, California 1.*

Dysentery (Bacillary)

13 cases: Mariposa County 1, Fullerton 1, San Francisco 2, Daly City 1, Tulare County 8.

Leprosy

One case: LaVerne.

Poliomyelitis

38 Cases: Oakland 5, Piedmont 1, Fresno County 2, Los Angeles County 3, Beverly Hills 1, Glendale 1, Los Angeles 5, San Fernando 1, Madera County 1, Marin County 1, Nevada County 2, Colfax 1, Sacramento 2, Chula Vista 1, San Diego 1, San Joaquin County 2, Stockton 1, Tulare County 6, Dinuba 1.

Tetanus

One case: Long Beach.

Encephalitis

8 cases: Fresno County 1, Fresno 1, Selma 1, Kern County 1, North Sacramento 1, San Jose 1, Tulare County 1, Davis 1.

Paratyphoid Fever

One case: Sonoma County.

Rocky Mt. Spotted Fever

One case: California.*

Typhus Fever

One case: Los Angeles.

Jaundice (Epidemic)

One case: El Dorado County.

Food Poisoning

13 cases: Monterey County 3, Monterey 6, Hillsborough 4.

Undulant Fever

6 cases: Colusa County 1, Clovis 1, Imperial County 1, Kern County 1, Monrovia 1, Palo Alto 1.

Tularemia

One case: California.*

Coccidioidal Granuloma

One case: Fresno County.

Rabies (Animal)

34 cases: Fresno County 2, Fresno 1, Los Angeles County 1, Burbank 1, El Segundo 1, Long Beach 1, Los Angeles 17, Pasadena 1, Pomona 2, Redondo Beach 1, Santa Monica 1, West Covina 1, San Bernardino 1, Manteca 2, Santa Cruz County 1.

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* Cases charged to "California" represent patients ill before entering the state or those who contracted their illness traveling about the state throughout the incubation period of the disease. These cases are not chargeable to any one locality.

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